

Correlation of diuretic therapy toward *clinical outcome* of patients suffering from chronic kidney disease hospitalized in RSUP DR. M. Djamil Padang

Fathnur Sani K^{*1}, Armenia², Aina Fatkhil Haque¹

¹ Pharmacy Academy of Al-Fatah Bengkulu

Jl. Indragiri Gang 3 Serangkai Padang Harapan Bengkulu

² Faculty of pharmacy Andalas University

Jl. Limau Manis, Limau Manis, Pauh, Kota Padang, Sumatera Barat

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ABSTRACT

Kidney is one of the most important organs of the human body. The goal of diuretic therapy is to reduce edema in patients with kidney functional disorder. The measure of the diuretic therapy is rather important because the effective usage can help in controlling the volume of extracellular fluid, in reducing protein excretion in urine, and in reducing the effects of hyperkalemia so that it can prevent the emergence of other cardiovascular complications. The purpose of this research is to provide the information of the effect of giving diuretics toward clinical outcome of patients with chronic kidney disease. The research was conducted by using longitudinal observational study design. Longitudinal observation is a method that performs data retrieval by a prospective census method with daily follow up until patient returns. The result of research showed that the most widely used diuretic was furosemide, then the results also showed improvement of blood pressure, pulse, respiration rate, creatinine, and urea although statistically not all undertook the significant change ($p > 0.05$). The result of patient outcome also showed mortality rate of the subjects in RSUP DR. M. Djamil Padang Hospital was very small. The patients with diuretic and without diuretic have equal mortality rate due to this disease ($p > 0.05$).

Keywords: kidney, CKD, outcome, diuretic

Correspondence author:

Fathnur Sani K

Pharmacy Academy of Al-Fatah Bengkulu

Jl. Indragiri Gang 3 Serangkai Padang Harapan Bengkulu

Email: fathnursani19@gmail.com

INTRODUCTION

Kidney is one of the most important organs of the human body. This organ functions to sustain balance including chemical and physical balance. Besides, the kidney also works to excrete metabolic substances which are dangerous to the body such as urea, creatinine, and ammonia (Baradero, *et al.*, 2009). If the kidney is disturbed, nephrons are not able to effectively absorb some substrates which were supposed to be reabsorbed, like albumin, protein, and glucose. If this continues for quite some time, it will cause the disorder of body electrolyte removal process and red blood cell production. As a result, it will trigger other disease complications such as anemia, hypertension, infections, and so forth (Popat, 2011; Jha, *et al.*, 2013).

The chronic kidney disease attracts attention more, and it is more studied because though the patient has reached the final stage, the patient can still live long with a good quality of life and its improved prevalence throughout the year (Tandi, 2014).

The case of kidney functional disorder in the world increased more than 50%, while in Indonesia it had reached 20% of the population (Suhardjono, 2007). In Malaysia, of all 18 million people there were 1800 new cases of kidney failure each year (Allan, 2009). In United States based on the data in 2008 from *United States Renal Data System* (USRDS) there were 33 million Americans or around 16% of the number of population suffering kidney disease. From this amount about 550.000 patients ran dialysis process or kidney transplant to survive their lives, while 88.620 people died. Approximately, this incident would keep increasing every year (Gaber, 2011).

According to the pre-survey result in RSUP DR. M. Djamil toward the medical records of patients hospitalized in the wards of internal diseases and functional disorders from 2011-2013, it showed in 2011 there were 110 patients, in 2012 there were 167 patients suffering from kidney functional disorder, and in 2013 there were 268 patients suffering from kidney functional disorder. This survey showed there was a growth of prevalence of patients with kidney functional disorder year by year in RSUP DR. M. Djamil Padang.

The increase of prevalence of patients with kidney functional disorder was caused by many factors starting from a sedentary lifestyle, less drinking, a dietary habit of high fat and carbohydrates, and bad environment. This would cause the occurrence of metabolic disorders that led to degenerative kidney disease (Alam and Hadibroto, 2007). Besides, the other causes could derive from the age factor, the presence of comorbidities like diabetes, hypertension, and urinary tract infection, the use of nephrotoxic drugs, and so on (Lemeire, *et al.*, 2006; Allan, 2013).

The diuretic therapy aimed to reduce edema on the patients with kidney functional disorder. The measure of giving diuretic was rather vital because its effective use could help in controlling the volume of extracellular fluid, in reducing the protein excretion in urine, and in reducing the hyperkalemia effect so that it could prevent the emergence of other cardiovascular complications (Suwitra, 2007; National Institute for Health and Care Excellence, 2015). However, in a particular circumstance the use of diuretic therapy became ineffective because of diuretic resistance like on the patients with kidney functional discharge (Golikorsky, 2007). This could aggravate kidney work by the increase of chemical substances entering the kidney (Sica, 2011).

Based on the above issues the researcher was interested in carrying out a research of correlation of giving diuretic toward *Clinical outcome* of patients with kidney functional disorder at the rate of 47 research samples in RSUP DR. M. Djamil Padang so that it could give information of the influence of giving diuretic toward *Clinical outcome* of patients with chronic kidney disease.

MATERIALS AND METHODS

Research Type

The research was done by using the longitudinal observational study design. Longitudinal observation was a method that performed the data collection by a prospective census method

accompanied with *follow up* every day until the patients went home. This research applied the analytic approach in collecting the result.

Stipulation of Patients Criteria to be Evaluated

The research samples were all the populations that met the criteria in this research, which were 47 patients.

Inclusion Criteria

Inclusion criteria were all medical records of patients with kidney functional disorder hospitalized in the ward of internal diseases in RSUP DR. M. Djamil Padang.

Exclusion Criteria

Exclusion criteria were the patients with kidney functional disorder of stage 5 which were hemodialyzed.

Research Variables

The research variables consisted of:

- a. Dependent variables included: *Clinical Outcome* (laboratory value of kidney function (chloride, potassium, sodium, anion gap, ureum, creatinine, and mortality of patients with Chronic Kidney Disease).
- b. Independent Variables included: gender, age, and diuretic.

Operational Definitions

1. Diuretic is a drug that increases the rate of urine formation on the patients with kidney functional disorder, such as furosemide, spironolactone, hydroxloriazide, and their combination.
2. *Clinical out come* is patient clinical outcome toward the diuretic therapy applied as seen from vital signs, edema, drinking volume, urine volume, patient's weight, and laboratory result of renal function. The data is obtained from observational result of medical record and patient's *follow up*.
3. Kidney functional disorder is a decrease on renal function marked by the increase of creatinine in blood serum and the decline of renal filtration rate that happens within more than 3 months.
4. Before is the measurement of patient's data first entering the hospital before getting therapy.
5. During is the measurement during treatment.
6. After is the last measurement when the patient is discharged from the hospital.

Data Collection Procedure

Data collection was done through noting the patients' medical record including gender, age, patient's diagnosis, diuretic medication for chronic kidney disease, vital signs (blood pressure, pulse, and respiration rate), laboratory value of kidney function (chloride, potassium, sodium, anion gap, ureum, and creatinine).

Data Analysis

For the research result data analysis would be conducted by using univariate analysis, namely the descriptive data of percentage of patient characteristics, drug distribution, and characteristics of vital signs, the condition of the electrolyte, and kidney function laboratory. Then, bivariate test was performed, such as *Chi Square* test to determine the value of the significance of each measurement and *Odd Ratio* testing on the mortality measurement of the patients with chronic kidney disease by using SPSS program with 95% confidence level ($p < 0.05$).

RESULT AND DISCUSSION

General Characteristics

General characteristics of the patients including Gender, Age, and Diagnosis were presented in Table I. The research was done in RSUP DR. M. Djamil Padang with a sample of 47 patients. Based on the data the patients that met the requirements for this study amounted to 47 people, and most of these patients were male (65.95%). The findings of the above data were in accordance with the research that had been done by Nuraeni, *et al.*, (2013). It was caused by several factors, such as lifestyle (food, beverages, and smoking) and the presence of high levels of stress in males (Kenward and Tan, 2003). In addition, women had the estrogen hormone that could act as antioxidants that could protect the activities of the glomerulus hemodynamics (Gibney, 2005). This amount was also eligible for the statistical analysis test by using SPSS program. According to Nursalam (2003) and Sani K. (2016) stated in their books the minimum number of samples in a research is 30.

Table I. General Characteristics of Patients with Chronic Kidney Disease in RSUP DR. M. Djamil Padang

	Characteristics	n (%)
Gender	Male	31 (65.96%)
	Female	16 (34.04%)
Age	< 45 years	4 (8.51%)
	45 – 54 years	13 (27.66%)
	55 – 64 years	18 (38.30%)
	> 65 years	12 (25.53%)
Diagnosis	CKD stage 3	11 (23.40%)
	CKD stage 4	14 (29.79%)
	CKD stage 5	22 (46.81%)
Risk Factors	Diabetes Mellitus	27 (57.45%)
	Hypertension	15 (31.91%)
	Autoimmune	2 (4.26%)
	Heart Failure	5 (10.64%)
	Smoking	20 (42.55%)

An increase of a person's age was followed by a decrease of function of the organs. The data of this research showed that the number of patients with kidney functional disorder increased on patients aged 55 – 65 years and over. The research result was reinforced by the studies conducted by Egberongbe, *et al.*, (2010) and Nuraeni, *et al.*, (2013). According to Chris (2007), at the age of 40-50 years and over the function of many organs including kidney had dropped, so that it was not surprising the result of this research reported a lot of people in the age over 55 years suffered from kidney functional disorder.

Most of the patients who were treated in RSUP DR. M. Djamil Padang came with a diagnosis of kidney functional disorder stage 5. It was because kidney functional disorder was an asymptomatic disease (it did not show clinical symptoms) in the early course of the disease so that when admission to a hospital the patient was already in a state of high severity (Kumboyono, *et al.*, 2010). This was in line with the result of research done by Wulandari (2013).

As previously explained there were many factors that caused the onset of kidney functional disorder. Based on the result of the previous studies conducted by Melanie, *et al.*, (2003) and Andrew, *et al.*, (2009) the risk factors that caused the patient to experience kidney functional disorder were diabetes mellitus, hypertension, heart failure, autoimmune, kidney stones, and smoking. This was in line with the result of this research showing the most risk factors of patients with kidney functional

disorder in RSUP DR. M. Djamil were diabetes mellitus, followed by smoking, cardiovascular disease (hypertension and heart failure), kidney stones, and autoimmune.

Correlation of Diuretic Therapy and Clinical Outcome of Patients with Kidney Functional Disorder

The distribution data of the therapy of diuretic drugs and the combinations (Table II) in patients with kidney functional disorder who were treated in the inpatient ward of the internal disease in RSUP DR. M. Djamil Padang showed that the majority of patients with kidney functional disorder got therapy furosemide therapy (63.83%), then it was followed by the patients who got spironolactone therapy, and the rest did not get the diuretic therapy.

Table II. Distribution of Use of Diuretic Drugs and the Combinations

Diuretic Drugs	Diagnosis			Total (%)	p Value
	CKD stage 3	CKD stage 4	CKD stage 5		
NoDiuretic	6	4	4	14 (29.78%)	0.082
Furosemide	4	7	15	26 (55.32%)	
Spironolactone	2	5	0	7 (14.89%)	
Total				47 (100%)	

Note: CKD: Chronic Kidney Disease, the p value was analyzed using *chisquare* statistic.

Diuretic therapy is quite important for patients with kidney functional disorder. The use of an effective diuretic can help in controlling the volume of extracellular fluid, reducing the excretion of protein in the urine and reducing the risk that would be caused by hyperkalemia. The considerations in the administration of a diuretic could be seen from the patient's condition such as edema and increase in blood pressure (Sica, 2011).

In this research, furosemide is the most diuretic given to the patients with kidney functional disorder stage 4 and 5 with a dose of 40-80 mg 1-2 times a day. This was in accordance with the studies done by Ernst and Gordon (2010) and Wulandari (2013). According to the guideline, the use of furosemide could be administered at all stages of kidney functional disorder. In pharmacokinetics and pharmacodynamics furosemide (loop diuretic) still provided the highest effectiveness in overcoming edema and oliguria that occurred in the patients with kidney functional disorder. The effectiveness of the sodium excretion was 20% and could still be efficient for low glomerular filtration rate (Dussol *et al.*, 2005).

The spironolactone diuretic was given to the patients with kidney functional disorder stage 1 to stage 3. This diuretic was given to the patients who needed a diuretic to reduce the fluid on their body, but received no extra potassium therapy from the outside, and did not experience hyperkalemia (Sica, 2011). From the result of the research conducted by Yuriawantini *et al.*, (2008), the provision of spironolactone also had a role in the process of decline in the value of albuminuria accompanied with a decrease in blood pressure on the patients with kidney functional disorder. This statement was also in accordance with the results of the research of Epstein (2001), Bianchi, *et al.* (2006) and Vecchio, *et al.* (2007).

Table III. Characteristics of the data of vital signs, electrolyte condition and laboratory of renal function before, during, and after the use of diuretics

Characteristics Monitored	Examination Results			p Value
	Before	During	After	
Systolic Blood Pressure (mmHg)	141.26	138.45	129.79	0.108
Diastolic Blood Pressure (mmHg)	82.13	80.98	77.30	0.183
Respiration Rate (/minute)	24.40	22.91	22.38	0.007*
Pulse (/minute)	91.55	89.66	87.21	0.153
Chloride (mmol/L)	103.21	102.93	102.47	0.900
Potassium (mmol/L)	4.25	3.88	3.63	0.001*
Sodium (mmol/L)	134.94	133.81	132.85	0.638
Anion Gap (mmol/L)	17.89	15.33	12.40	0.007*
Creatinine Clearance (mL/minute)	21.34	21.81	21.90	0.851
Ureum (mg/dL)	106.73	106.92	102.42	0.942

Note * : states there was a significant change between Before, During, and After
p value was analyzed by the *chi square* statistic type

A study conducted by Bakris, *et al.*, (2003) stated that patients with kidney functional disorder required diuretic therapy to achieve the target of blood pressure of < 140 mmHg. The result showed that there was an improvement in blood pressure becoming 129.79 mmHg although statistically it was not significant (Tables II and III). The effectiveness of diuretics could be assessed by the decrease of complaints of breathlessness, the heart rate improvement, and the fluid balance (Nancy and Vaughan, 2009). The most dominant diuretic applied to the patients with kidney functional disorder was furosemide although in certain conditions other diuretics were still in use (May, 2013).

The use of diuretics on the patients with kidney functional disorder could still provide the good effectiveness of prevention of cardiovascular disease. It could be seen from the decline in blood pressure (an average of 130/78 mmHg), the decrease of tightness, and the maintenance of the fluid balance (the value of water intake and urine volume of the patient). The result of this study was in accordance with the results of the study carried out by Maura (2006). The statement about the blood pressure was also in line with the report by Dipiro, *et al.*, (2005), Kumar, *et al.*, (2005), Jerry (2011), and Allan (2013) stating that the blood pressure target for the patients with kidney functional disorder was 130/80 mmHg. However, the research result showed the decline in blood pressure could also be influenced by the presence of additional therapy of other antihypertensive drugs that in this study would be discussed in the section on adjunctive therapy on the patients with kidney functional disorder. The research result also showed the decline in blood pressure would be in touch with the breath and heart rate of patients who returned to normal. This was in accordance with the results of the research by Rajiv (2009) and Wulandari (2013).

The most important thing to monitor to see the effectiveness of the administration of a diuretic is the value of the electrolyte. According to the theory, the patients with kidney functional disorder often had electrolyte disorders resulted from disruption of fluid balance in the body (Price and Wilson, 2005). In this research it was seen that an increase of the kidney disorder stage was very influential on the value of the electrolytes of the patients although in the therapy the value of the electrolyte was still within normal limits, and an insignificant decline occurred ($p > 0.05$), except for Potassium and Anion Gap ($P < 0.05$). This was in line with the result of research done by Wulandari (2013). The presence of this balance could be influenced by many factors, such as the use of drugs that had side effects that increased the levels of electrolytes in the blood. For example, the use of class of *angiotensin converting enzyme inhibitors* (ACEI) (captopril and ramipril). *ACE inhibitors* could cause hyperkalemia due to the decline of aldosterone which was a steroid hormone which worked to reabsorb sodium and chloride and to excrete potassium. If aldosterone was not produced because of the decrease of kidney function,

this led to an increase in the amount of potassium in blood. The decrease of aldosterone happened because of the unavailability of angiotensin II due to the inhibition of *angiotensin converting enzyme* by *angiotensin converting enzyme inhibitors*. This effect was usually not significant on the patients with normal renal function, but in patients with damage to the kidney function whose balance setting of the electrolyte had been interrupted, the increase of potassium could occur (Weber, 2001).

The use of diuretics of furosemide and spironolactone toward the decline in kidney function did not show a significant effect ($p > 0.05$). The value of ureum, creatinine, and creatinine clearance patients still remained high. This was in accordance with the result of the research by Wulandari (2013) on the patients with kidney functional disorder in Malaysia. This insignificant reduction not meaningful could be associated with the overcome of the risk factors and complications on the patients with kidney functional disorder. According to Wim (2006), the most important thing to prolong the life of patients with kidney functional disorder was to resolve or control the risk factors and the complications that arose (Wim, 2006).

The mortality data (Table IV) of the patients with kidney functional disorder treated in the inpatient ward of the internal diseases in RSUP DR. M. Djamil Padang showed that men were more at risk 2.154 times (CI: 0.382-12.152) experiencing death compared with women with $p > 0.05$. It identified the males and females had the same opportunities in term of mortality. This result was in accordance with the data created by Stephan and Stein (2008). He stated that the high risk on men was influenced by many factors, such as lifestyle, namely the presence of a history of smoking, stress, and genetic factors.

Table IV. Correlation of gender with mortality of patients with chronic kidney disease

Gender	Mortality		Odd Ratio (CI 95%)	p Value
	Life	Death		
Male	28	3	2.154 (0.382 – 12.152)	0.388
Female	13	3	0.464 (0.082 – 2.619)	

Note: p value was analyzed by the chi square statistic type

Mortality of patients based on age (Table V) of the patients with kidney functional disorder treated in the inpatient ward of the internal diseases in RSUP DR. M. Djamil Padang showed that the average patient checking out with age 57 ± 11.29 years and that the average of patients' age who died was 55 ± 7.12 year with $p > 0.05$.

Table V. Patients' mortality based on age

Mortality	N	Mean Age (Years) \pm SD	p Value
Checking out without complications	0	0	0.521
Checking out with complications	41	57 ± 11.29	
Death	6	55 ± 7.12	
Total	47		

Note: p value was analyzed by the *chi square* statistic type

Kidney function disorder generally occurred on the patients with older age (Garg, *et al.*, 2004). An increase of a person's age was followed by a decrease in all the functions of the organs including kidney so that it became vulnerable to diseases. The research result showed the average age of patients checking out with complications was 57 years and the average age of patients who died was 55 years. This was in accordance with the research of O'hare, *et al.*, (2007) who stated complications and death in patients with kidney functional disorder had been started from the age of 45 years, while

according to Kim, *et al.*, (2009) complications and death in patients with kidney functional disorder was started since the age of ≥ 65 years. This difference arose because in addition to age there were other things that triggered the kidney damage in a younger age i.e. the lifestyle and concomitant diseases in the patients with kidney functional disorder (Drey, *et al.*, 2003).

Mortality data (Table VI) of patients with kidney functional disorder treated in the inpatient ward of the internal diseases in RSUP DR. M. Djamil Padang showed that the use of diuretic therapy could increase the mortality by 1.061 compared with no use of diuretics. Though statistically they had the same opportunities i.e. $p > 0.05$.

Table VI. Correlation of Diuretic Therapy and Mortality of Patients with Chronic Kidney Disease

Therapy	Mortality		Odd Ratio (CI 95%)	p Value
	Life	Death		
No Diuretic	12	2	0.878 (0.257 – 2.997)	0.578
Diuretic	33	4	1.061 (0.583 – 1.931)	

Note: p value was analyzed by the type of *chi square* statistic

The data of Table VI showed that giving diuretic and no diuretic gave the same influence toward the mortality. It was because the patients with kidney functional disorder was the disease causing the decline of kidney functional gradually. Hypertension and water retention (edema) were the main issue that was very influential toward the patients' mortality. Hence, giving diuretic was what a doctor must consider during the therapy. Although it gave more influence on the nephron damage (Sinha and Aqarwal, 2015).

CONCLUSION

From the result of the research conducted it could be concluded as follows:

1. Nearly all parameters of patients' outcome did not change significantly during and after getting the diuretic therapy, except plasma potassium, respiration rate, and anion gap undertaking the decline significantly ($p < 0.05$).
2. Male patients and patients with diuretic had a bigger chance (OR = 2.154 and 1.061) to undertake mortality than female patients and patients without diuretic although statistically it was not significantly different ($p > 0.05$). Therefore, it showed that giving diuretic was only as the additional therapy to overcome the severe conditions of patients with kidney functional disorder like hypertension, asthma, and edema.

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